Accumulation of 2-Deoxy-2-[18F]Fluoro-D-Galactose in Well Differentiated Hepatoma of Mouse and Rats

III. 12. Accumulation of 2-Deoxy-2-[^{18}F]fluoro-D-Galactose in Well Differentiated Hepatoma of Mouse and Rat

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Occasionally, cancer cells express phenotypes of original tissues or organs. The degree of phenotype expression in the tumor may represent the degree of differentiation of cancer. If a radiolabeled tracer, which is a substrate for a specific enzyme of the tissue or organ is used, the cancer originating from the specific tissue should be detectable and the degree of phenotype expression, that is the degree of differentiation in cancer cells can be evaluated.

2-deoxy-2-[^{18}F]fluoro-D-galactose (^{18}F-FDGal) ia s positron labeled galactose analog, which is phospholylated by galactokinase and then trapped after the second metabolic step of the galactose pathway[1]. As substantially high activity of galactokinase is found only in the liver, it can be considered as a liver specific tracer and a new probe for the evaluation of galactose metabolism in the liver using PET[2,3]. We also found by preliminary PET study that ^{18}F-FDGal accumulates very high in hepatocellular carcinomas(HCC). In order to investigate the mechanism of the specific high accumulation of ^{18}F-FDGal in HCC, we examined the accumulation of ^{18}F-FDGal in a well differentiated, spontaneous hepatoma of C3H mouse and Morris rat hepatoma and compared it to that in poorly differentiated hepatomas and tumors other than hepatoma.

Materials and Methods

^{18}F-FDGal was synthesized by the reaction of tri-O-ascetyl-D-galactal and [^{18}F]CH3COOF[4,5].

A spontaneous hepatoma of C3H/HeMs mouse, which is slow growing and well differentiated histologically[6] was used for the biodistribution studies.

A Morris hepatoma of Buffalo rat, 5123D and the ascitic hepatomas of Donryu rat, AH109A and AH272 were also used for the biodistribution studies. The former is slow growing and well differentiated[7] and the latter two lines grow rapidly and are poorly differentiated histologically[8,9]. The cell suspension of 5123D was prepared from the excised tumors and the cells were inoculated subcutaneously into the back of baffalo rats. The ascitic tumor cells of AH109A and AH272 were inoculated subcutaneously into the back back of

Donryu rats. The experiments were performed when the tumor size became grater than 10mm in diameter. As tumors other than hepatoma, a mammary carcinoma of C3H mouse; FM3A and a melanoma of C57BL mouse; B-16 were also used.

^{18}F-FDGal (370KBq in 0.2ml isotonic saline) was injected into the mouse or rat through the lateral vein. Then tissues and tumor were removed, blotted and weighed. The radioactivity in the tissues was counted by NaI automated counter decay-corrected and expressed as %dose/g or differential absorption ratio (DAR).

Results

Table 1 shows the biodistribution of ^{18}F-FDGal and tumor-to-tissue ratios in the HCC bearing C3H mouse. The accumulation of ^{18}F-FDGal in the normal liver rapidly increased with time and reached a near plateau by 10min. The value at 60min was 20.1%dose/g. The tumor uptake was also very high and gradually increased with time. The value was 18.4% dose/g at 60min and 92% of that in the liver.

Table 2 shows the biodistribution of ^{18}F-FDGal and tumor-to-tissue ratios in 5123D bearing rat. The uptake both in the normal liver and the tumor was high and increasd with time. The value at 60min was 7.90% dose/g. The accumulation of ^{18}F-FDGal in the tumor reached a near plateau by 10min. The value was 2.58% dose/g at 60min and 33% of that in the liver. The tumor-to-liver ratio at 60min was lower than that in C3H hepatoma.

Table 3 shows the biodistribution of ^{18}F-FDGal and the tumor-to-tissue ratios in AH109A bearing rat. The liver uptake reached a near plateau at 30min and the value was 8.54 %dose/g at 60min after injection. Tumor uptake gradually increased with time and reached a near plateau at 60min with a value of 1.37%dose/g. The tumor-to-liver ratio at 60min was much lower than those in C3H hepatoma and 5123D.

Table 4 shows the tumor uptake and tumor-to-liver ratios at 60min im various tumors which we examined in the present experiments. The tumor uptake were expressed by DAR in addition to %dose/g. Among the tumors, the uptake of C3H hepatoma was highest and the 5123D was the second to C3H hepatoma. On the other hand, those of poorly differentiated rat hepatomas and tumors other than hepatoma were very low. The tumor-to-liver ratio was extremely high in the C3H hepatoma and relatively high in 5123D.

Discussion

The biodistribution studies in tumor bearing mouse and rats showed that the accumulation was exclusively high in C_3H hepatoma and relatively high in 5123D among the tumors. While that in poorly differentiated hepatomas and tumors other than hepatoma were low.

Bauer et al.[9] examined the change in the galactose metabolism in experimental hepatomas and compared it with that in the normal liver. They found a decrease in galactose uptake and an increase of UDP-galactose 4'-epimerase in relation to the tumor growth rate. That means well differentiated hepatomas maintain galactose metabolic enzymes but these enzymes are

possibly lost as the tumor growth becomes rapid or the tumor becomes malignant. Their report can be considered supporting data for the high accumulation of ^{18}F-FDGal in C3H hepatoma and 5123D.

We found preliminary clinical PET study that ^{18}F-FDGal accumulation is very high in HCC which originates from hepatocell, but very low in metastatic liver tumors.[10,11] This also may be a clinical evidence for the hypothesis.

In conclusion, the ^{18}F-FDGal uptake may represent a galactose metabolism in the tumor and PET study with ^{18}F-FDGal can be employed for the detection and biochemical characterization of HCC and differential diagnosis between HCC and metastatic liver tumor. The final goal of this study is to devise a new method for in vivo characterization of HCC using ^{18}F-FDGal as an indicator of galactose metabolism.

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Table 1. F-18 Radioactivity Following Injection of 2-Deoxy-2 [^{18}F]- Fluoro-D-Galactose in Spontaneous Hepatoma BearingC_3H Mice.

Organ	Uptake (% dose/g)*			
	2 min	10min	30 min	60 min
Tumor	10.1 ± 1.74	11.9 ± 2.17	14.1 ± 6.83	18.4 ± 3.14
Blood	3.92 ± 1.02	2.15 ± 0.65	1.48 ± 0.36	1.45 ± 0.15
	(2.59)#	(5.50)	(9.50)	(12.7)
Heart	4.97 ± 0.98	3.93 ± 1.03	3.09 ± 0.52	3.13 ± 0.99
	(2.04)	(3.02)	(4.56)	(5.90)
Liver	10.2 ± 2.90	18.1 ± 2.63	18.0 ± 4.78	20.1 ± 2.79
	(1.01)	(0.66)	(0.78)	(0.92)
Kidney	13.3 ± 2.73	12.7 ± 3.78	13.3 ± 2.21	14.6 ± 2.04
	(0.76)	(0.93)	(1.36)	(1.26)
Brain	2.13 ± 0.35	2.24 ± 0.55	2.18 ± 1.47	2.83 ± 0.30
	(4.76)	(5.29)	(6.46)	(6.51)
Muscle	1.65 ± 0.27	0.95 ± 0.29	0.91 ± 0.32	0.76 ± 0.30
	(6.15)	(12.5)	(15.5)	(24.2)

*: Mean value obtained from 5-7 mice ± SD
#: Tumor-to-tissue ratio.

Table 2. F-18 Radioactivity Following Injection of 2-Deoxy-2-[^{18}F]-Fluoro-D-Galactose in Morris Rat Hepatoma (5123D).

Organ	Uptake (% dose/g)*			
	2 min	10min	30 min	60 min
Tumor	1.52 ± 0.44	2.38 ± 0.06	2.31 ± 0.63	2.58 ± 0.40
Blood	1.14 ± 0.20	0.68± 0.02	0.28± 0.05	0.27 ± 0.02
	(1.33) #	(3.50)	(8.25)	(9.56)
Heart	0.70± 0.10	0.72 ± 0.08	0.48 ± 0.07	0.52 ± 0.07
	(2.17)	(3.31)	(4.81)	(4.96)
Lung	0.75± 0.16	0.52 ± 0.04	0.30 ± 0.05	0.35 ± 0.06
	(2.03)	(4.58)	(7.70)	(7.37)
Liver	3.53 ± 0.97	6.90 ± 0.46	7.23 ± 0.69	7.90 ± 0.74
	(0.43)	(0.34)	(0.32)	(0.33)
Kidney	3.47 ± 0.74	4.01± 0.62	3.54 ± 0.89	4.10 ± 0.50
	(0.44)	(0.59)	(0.65)	(0.63)
Brain	0.54 ± 0.05	0.69 ± 0.06	0.64± 0.08	0.78± 0.07
	(2.81)	(3.45)	(3.61)	(3.31)
Muscle	0.33 ± 0.09	0.25 ± 0.04	0.20 ± 0.08	0.26 ± 0.07
	(4.60)	(9.52)	(11.6)	(9.92)

*: Mean value obtained from 6 rats ± SD.
#: Tumor-to-tissue ratio.

Table 3. F-18 Radioactivity Following Injection of 2-Deoxy-2-[^{18}F]- Fluoro-D-Galactose in Hepatoma (AH109A) Bearing Rats

Organ	Uptake (% dose/g)*			
	10 min	30min	60 min	120 min
Tumor	0.89 ± 0.19	1.08 ± 0.26	1.37 ± 0.17	1.41 ± 0.13
Blood	0.53 ± 0.04	0.29 ± 0.02	0.26 ± 0.04	0.24 ± 0.02
	(1.68) #	(3.72)	(5.27)	(5.88)
Heart	0.63 ± 0.03	0.34 ± 0.03	0.34 ± 0.04	0.34 ± 0.05
	(1.41)	(3.18)	(4.03)	(4.15)
Lung	0.55 ± 0.01	0.43 ± 0.08	0.33 ± 0.07	0.29 ± 0.02
	(1.62)	(2.51)	(4.15)	(4.86)
Liver	5.60 ± 0.39	8.00 ± 0.68	8.54 ± 0.84	7.96 ± 0.42
	(0.16)	(0.14)	(0.16)	(0.18)
Kidney	3.10 ± 0.34	3.10± 0.26	2.81 ± 0.36	2.49 ± 0.19
	(0.29)	(0.35)	(0.49)	(0.57)
Brain	0.56 ± 0.03	0.66 ± 0.06	0.68 ± 0.07	0.72 ± 0.04
	(1.59)	(1.64)	(2.01)	(1.96)
Muscle	0.18 ± 0.01	0.11 ± 0.02	0.10 ± 0.02	0.10 ± 0.03
	(4.94)	(9.82)	(13.7)	(14.1)

*: Mean value obtained from 6 rats ± SD
#: Tumor-to-tissue ratio.

Table 4 Tumor uptake and tumor-to-liver ratios of 2-Deoxy-2-[^{18}F] Fluoro-D-galactose in various tumors

Tumor	Animal	Uptake at 60 min*		
		% dose/g	DAR#	Tumor/Liver
HCC	C3H	18.4 ± 3.14	6.86 ± 1.18	0.92
5123D	Baffalo	2.58 ± 0.40	3.53 ± 0.74	0.33
AH272	Donryu	1.51 ± 0.20	1.86 ± 0.21	0.18
AH109A	Donryu	1.37 ± 0.20	1.75 ± 0.12	0.16
FM3A	C3H	6.37 ± 0.50	1.40 ± 0.09	0.18
B-16	C57BL	4.53 ± 0.83	1.13 ± 0.17	0.14
Liver				
	C3H @	20.1 ± 2.79	7.99 ± 1.47	
	C3H§	35.2 ± 4.10	8.80 ± 0.88	
	Baffalo	7.90 ± 0.74	10.8 ± 1.26	
	Donryu	8.54 ± 0.84	13.8 ± 1.40	
	C57BL	32.7 ± 2.40	8.18 ± 0.80	

*: Mean value obtained from 4-6 animals ± SD.
: DAR=Tissue activity(cpm/g)/Injected dose(cpm)/body weight(g)
@ 15-17 months old (body weight; 35-43g)
§: 10-week-old (body weight; 27-32g)